In Vitro Activities of Tedizolid and Linezolid against Gram-Positive Cocci Associated with Acute Bacterial Skin and Skin Structure Infections and Pneumonia

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Tedizolid is a novel, expanded-spectrum oxazolidinone with potent activity against a wide range of Gram-positive pathogens. A total of 425 isolates of Gram-positive bacteria were obtained consecutively from patients with acute bacterial skin and skin structure infections (ABSSSIs) or pneumonia. These isolates included methicillin-susceptible *Staphylococcus aureus* (MSSA) ($n = 100$), methicillin-resistant *Staphylococcus aureus* (MRSA) ($n = 100$), *Streptococcus pyogenes* ($n = 50$), *Streptococcus agalactiae* ($n = 50$), *Streptococcus anginosus* group ($n = 75$), *Enterococcus faecalis* ($n = 50$), and vancomycin-resistant enterococci (VRE) (*Enterococcus faecium*) ($n = 50$). The MICs of tedizolid and linezolid were determined by the agar dilution method. Tedizolid exhibited better *in vitro* activities than linezolid against MSSA (MIC₉₀s, 0.5 versus 2 μ g/ml), MRSA (MIC₉₀s, 0.5 versus 2 μ g/ml), *S. pyogenes* (MIC₉₀s, 0.5 versus 2 μ g/ml), *S. agalactiae* (MIC₉₀s, 0.5 versus 2 μ g/ml), *Streptococcus anginosus* group (MIC₉₀s, 0.5 versus 2 μ g/ml), *E. faecalis* (MIC₉₀s, 0.5 versus 2 μ g/ml), and VRE (MIC₉₀s, 0.5 versus 2 μ g/ml). The tedizolid MICs against *E. faecalis* ($n = 3$) and VRE ($n = 2$) intermediate to linezolid (MICs, 4 μ g/ml) were 1 μ g/ml and 0.5 μ g/ml, respectively. The tedizolid MIC₉₀s against *S. anginosus*, *S. constellatus*, and *S. intermedius* were 0.5, 1, and 0.5 μ g/ml, respectively, and the rates of susceptibility based on the U.S. FDA MIC interpretive breakpoints to the isolates were 16%, 28%, and 72%, respectively. Tedizolid exhibited 2- to 4-fold better *in vitro* activities than linezolid against a variety of Gram-positive cocci associated with ABSSSIs and pneumonia. The lower susceptibilities of tedizolid against isolates of *S. anginosus* and *S. constellatus* than against those of *S. intermedius* in Taiwan were noted.

Hospital- and community-acquired infections due to multi-drug-resistant (MDR) Gram-positive bacteria continue to be associated with high rates of morbidity and mortality (1–4). Infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are of particular concern (1–4). The recent emergence of MRSA, coagulase-negative staphylococci, and VRE with reduced susceptibilities to linezolid has been widely reported (5, 6). Tedizolid (formerly tordezolid) is a novel, expanded-spectrum oxazolidinone with potent activity against a wide range of Gram-positive pathogens, including MRSA, VRE, *Streptococcus pneumoniae*, beta-hemolytic streptococci, viridans group streptococci, and some linezolid-resistant strains (7–10). Tedizolid has been shown to be effective in the treatment of acute bacterial skin and skin structure infections (ABSSSIs) as well as hospital-acquired and ventilator-associated bacterial pneumonia and was approved by the U.S. Food and Drug Administration (FDA) in 2013 for the treatment of ABSSSIs caused by susceptible isolates of *S. aureus* (including MRSA and methicillin-susceptible *S. aureus* [MSSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, members of the *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*), and *Enterococcus faecalis* (7, 11–15). Although clinical experience with tedizolid remains limited, early data suggest that it is effective in the treatment of serious infections due to MDR Gram-positive pathogens (2, 7).

The aim of this study was to assess the *in vitro* activities of tedizolid and linezolid against commonly encountered clinical isolates of Gram-positive cocci associated with ABSSSIs and pneumonia.

MATERIALS AND METHODS

Bacterial isolates. A total of 425 isolates of Gram-positive bacteria were obtained consecutively from patients with ABSSSIs or pneumonia who were treated at the National Taiwan University Hospital (NTUH) from January 2013 to October 2014. The isolates were recovered from various clinical specimens, including pus from skin, wounds, and subcutaneous lesions (abscess), purulent sputum, pleural effusion, bronchoalveolar lavage fluid, and blood (associated with ABSSSIs or pneumonia). The recovered isolates included methicillin-susceptible *S. aureus* (MSSA) ($n = 100$), MRSA ($n = 100$), *S. pyogenes* ($n = 50$), *S. agalactiae* ($n = 50$), and *E. faecalis* ($n = 50$), and 25 isolates of each of the three species of the *S. anginosus* group (*S. anginosus*, *S. intermedius*, and *S. constellatus*). An additional 50 blood isolates of VRE (*E. faecium*) collected during the same time period from the NTUH were also included in this study. These isolates were identified by the conventional identification methods and the Phoenix system (Becton-Dickinson Diagnostic Systems, Sparks, MD). Susceptibility testing of these isolates to antimicrobial agents other than tedizolid and linezolid was also performed with the Phoenix system (Bec-

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TABLE 1 MIC distribution and susceptibility of 475 Gram-positive cocci isolated from patients with acute bacterial skin and skin structure infections or pneumonia to tedizolid and linezolid

Bacteria	No.	Agent	No. (cumulative %) of isolates for MIC (μg/ml) of:							MIC ₅₀ /MIC ₉₀ (μg/ml)	% of isolates			
			0.03	0.06	0.12	0.25	0.5	1	2		4	Susceptible	Intermediate	Resistant
Methicillin-susceptible <i>S. aureus</i>														
ABSSSI ^a	50	Tedizolid				19 (38)	31 (100)				0.25/0.5	100 ^b	0	
		Linezolid							48 (96)	2 (100)	2/2	100		0
Pneumonia	50	Tedizolid				16 (34)	34 (100)				0.5/0.5	100 ^b	0	
		Linezolid							50 (100)		2/2	100		0
Methicillin-resistant <i>S. aureus</i>														
ABSSSI	50	Tedizolid				49 (98)	1 (100)				0.25/0.25	100 ^b	0	
		Linezolid						12 (24)	37 (98)	1 (100)	1/2	100		0
Pneumonia	50	Tedizolid				15 (35)	35 (100)				0.5/0.5	100 ^b	0	
		Linezolid						2 (4)	48 (100)		2/2	100		0
<i>Streptococcus pyogenes</i>	50	Tedizolid			1 (2)	24 (50)	25 (100)				0.25/0.5	100 ^b		
		Linezolid						8 (16)	42 (100)		2/2	100		
<i>Streptococcus agalactiae</i>	50	Tedizolid				6 (12)	44 (100)				0.5/0.5	100 ^b		
		Linezolid						4 (8)	48 (100)		2/2	100		
<i>Streptococcus anginosus</i> group	75	Tedizolid	1 (0.3)	3 (8)	5 (14.7)	18 (38.7)	41 (93.3)	5 (100)			0.5/0.5	38.7 ^b		
		Linezolid				1 (1.3)	4 (6.7)	14 (25.3)	56 (100)		2/2	100		
<i>Streptococcus anginosus</i>	25	Tedizolid				4 (16.0)	21 (100)				0.5/0.5	16.0 ^b		
		Linezolid						3 (12)	22 (100)		2/2	100		
<i>Streptococcus constellatus</i>	25	Tedizolid			1 (4)	6 (28)	16 (92)	2 (100)			0.5/1	28 ^b		
		Linezolid						3 (12)	22 (100)		2/2	100		
<i>Streptococcus intermedius</i>	25	Tedizolid	1 (4)	5 (24)	4 (40)	8 (72)	4 (88)	3 (100)			0.25/0.5	72 ^b		
		Linezolid				1 (4)	4 (20)	8 (52)	12 (100)		1/2	100		
<i>Enterococcus faecalis</i>	50	Tedizolid				3 (6)	37 (80)	10 (100)			0.5/0.5	80 ^b		
		Linezolid						13 (26)	34 (94)	3 (100)	2/2	94	6	0
Vancomycin-resistant <i>Enterococcus faecium</i>	50	Tedizolid				8 (16)	42 (100)				0.5/0.5	100 ^b		
		Linezolid						6 (12)	42 (96)	2 (100)	2/2	96	4	0

^a ABSSSI, acute bacterial skin and skin structure infection.^b No Clinical and Laboratory Standards Institute MIC interpretive breakpoints for susceptibility are available (17). The susceptibility breakpoints of tedizolid recommended by the U.S. FDA were used. Only susceptible FDA breakpoints exist for all organisms other than *S. aureus*. These breakpoints are as follows: ≤ 0.5 $\mu\text{g/ml}$ for *S. aureus*, with an intermediate breakpoint at 1 $\mu\text{g/ml}$; ≤ 0.5 $\mu\text{g/ml}$ for *S. pyogenes*, *S. agalactiae*, and *E. faecalis*; and ≤ 0.25 $\mu\text{g/ml}$ for the *S. anginosus* group (15).

TABLE 2 MIC distribution and susceptibility of 75 isolates of *Streptococcus anginosus* group recovered from various clinical specimens of patients with acute bacterial skin and skin structure infections or pneumonia to tedizolid and linezolid

Source of isolates	No. of isolates	Agent	No. (cumulative %) of isolates for MIC (μg/ml) of:								MIC ₅₀ /MIC ₉₀ (μg/ml)	No. (%) susceptible
			0.03	0.06	0.12	0.25	0.5	1	2	4		
Pleural effusion	13	Tedizolid	1 (7.7)	2 (23.1)	1 (30.8)	3 (53.8)	4 (84.6)	2 (100)			0.25/1	7 (53.8)
		Linezolid				1 (7.7)	1 (15.4)	3 (38.5)	8 (100)		2/2	13 (100)
Skin pus, wound, abscess	18	Tedizolid		2 (11.1)	2 (22.2)	2 (33.3)	12 (100)				0.5/0.5	6 (33.3)
		Linezolid					1 (5.6)	3 (22.2)	14 (100)		2/2	18 (100)
Blood	44	Tedizolid		1 (2.3)	2 (6.8)	13 (36.4)	25 (93.2)	3 (100)			0.5/0.5	16 (36.4)
		Linezolid					2 (4.5)	8 (22.7)	34 (100)		2/2	44 (100)

ton-Dickinson Diagnostic Systems). The isolates were stored at –70°C in Trypticase soy broth (BBL Microbiology Systems, Cockeysville, MD, USA) supplemented with 15% glycerol before testing. The MICs of vancomycin against MRSA were also determined by the agar dilution method. This study was approved by the NTUH Institutional Review Board (NTUH-IRB-201411040).

Antimicrobial susceptibility testing. The MIC values of tedizolid (Cubist Pharmaceuticals, Lexington, MA) and linezolid (Pfizer Inc., New York, NY) against the isolates were determined using the agar dilution method according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) (16). The concentrations of both agents ranged from 0.015 to 32 μg/ml. *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619 were used as control strains. The MIC breakpoints used in this study to define the susceptibilities of tested organisms to linezolid were provided by the CLSI (17). For tedizolid, CLSI MIC interpretive breakpoints were not available (17).

The MIC interpretive breakpoints for tedizolid adopted by the U.S. FDA were derived from MIC population distributions, pharmacokinetic/pharmacodynamic information, including target attainment by Monte Carlo simulation, and clinical and microbiologic outcome data from clinical trials (15). In this study, the susceptibility breakpoints of tedizolid recommended by the U.S. FDA were used. These breakpoints are as follows: ≤0.5 μg/ml for *S. aureus*, with an intermediate breakpoint at 1 μg/ml; ≤0.5 μg/ml for *S. pyogenes*, *S. agalactiae*, and *E. faecalis*; and ≤0.25 μg/ml for the *S. anginosus* group (15).

RESULTS

The MIC values of linezolid against the three control strains were within the quality control ranges. The tedizolid MIC values were also within the quality control ranges: *S. aureus* ATCC 29213, 0.25 to 1 μg/ml; *E. faecalis* ATCC 29212, 0.5 μg/ml; and *S. pneumoniae* ATCC 49619, 0.12 to 0.25 μg/ml (15, 17).

Table 1 shows the MIC distribution and susceptibility to tedizolid and linezolid of 475 Gram-positive cocci isolated from patients with ABSSSIs or pneumonia. Tedizolid exhibited better *in vitro* activities than linezolid against MSSA (MIC₉₀s, 0.5 versus 2 μg/ml), MRSA (MIC₉₀s, 0.5 versus 2 μg/ml), *S. pyogenes* (MIC₉₀s, 0.5 versus 2 μg/ml), *S. agalactiae* (MIC₉₀s, 0.5 versus 2 μg/ml), *Streptococcus anginosus* group (MIC₉₀s, 0.5 versus 2 μg/ml), *E. faecalis* (MIC₉₀s, 0.5 versus 2 μg/ml), and VRE (MIC₉₀s, 0.5 versus 2 μg/ml). All isolates were susceptible to linezolid with the exception of three isolates of *E. faecalis* and two isolates of VRE (*E. faecium*), which showed intermediate resistance to linezolid (MICs of 4 μg/ml). The tedizolid MICs were 1 μg/ml for the three linezolid-intermediate *E. faecalis* isolates. The MIC values of tedizolid for the two isolates of linezolid-intermediate VRE (*E. faecium*) were 0.5 μg/ml. Four isolates of MRSA with intermediate

resistance to vancomycin (MICs of 4 μg/ml), all confirmed by the agar dilution method, exhibited a linezolid MIC of 2 μg/ml and a tedizolid MIC of 0.5 μg/ml.

Based on the tedizolid MIC breakpoints recommended by the U.S. FDA, all *S. aureus* isolates tested, including MSSA and MRSA, and 80% of *E. faecalis* isolates tested were susceptible to tedizolid. The MICs of tedizolid were slightly lower than those of linezolid for ABSSSIs and pneumonia between MRSA and MSSA.

Overall, a large percentage (61.3%) of *S. anginosus* group isolates were not susceptible to tedizolid, particularly isolates of *S. anginosus* (84%) and *S. constellatus* (72%). The rates of susceptibility to tedizolid for *S. anginosus* group isolates were higher (54%) from respiratory specimens (pleural effusion, *n* = 13) than from skin and skin structure specimens (pus, wound, or abscess, *n* = 18) (33%) and blood specimens (*n* = 44) (36%). The three linezolid-intermediate *E. faecalis* isolates also were not susceptible to tedizolid. However, the rates of susceptibility of the three species in the *S. anginosus* group were lower than those to linezolid (Table 2).

DISCUSSION

The findings in this study on the susceptibility of MSSA, MRSA, and enterococci to tedizolid are in agreement with those reported in other studies (7, 10, 14, 18). Tedizolid exhibited 2- to 4-fold better *in vitro* activities against the tested Gram-positive cocci than linezolid. An alarming finding in this study was the lower rate of susceptibility of *S. anginosus* group isolates to tedizolid. Among the tested isolates of the three species of the *S. anginosus* group, tedizolid exhibited lower activities against *S. anginosus* and *S. constellatus* than against *S. intermedius* based on the tedizolid MIC breakpoints proposed by the U.S. FDA (15).

Prokocimer et al. reported that among the 15 isolates of viridans group streptococci (the species of the isolates was not classified), tested in their study, tedizolid MICs ranged from 0.03 μg/ml to 0.25 μg/ml and linezolid MICs ranged from 0.12 μg/ml to 1 μg/ml (14). Zurenko et al. investigated the susceptibilities of the 91 isolates of the *S. anginosus* group to linezolid and tedizolid and found that all isolates were inhibited by tedizolid at 0.25 μg/ml (all susceptible) and by linezolid at 1 μg/ml (19). The MICs of linezolid against the *S. anginosus* group (categorized as members of viridans group streptococci) were 2-fold higher in our study than in the studies by Prokocimer et al. and Zurenko et al. (14, 19). However, the MICs of tedizolid against the *S. anginosus* group in our study were 4-fold higher than in those two previously reported studies (14, 19). These resulted in the high rates of tedizolid non-

susceptibility (MICs of ≥ 0.5 $\mu\text{g/ml}$) found in the present study. Isolates of the *S. anginosus* group studied by Zurenko et al. were recovered from annual surveillance programs in Europe, from 3 clinical trials of tedizolid for treatment of ABSSSI, and from a preclinical study of tedizolid activity (19). In this study, although the majority (58.7%) of *S. anginosus* group isolates were recovered from patients with bacteremia associated with ABSSSIs or pneumonia, the highest rate of nonsusceptibility (66.7%) was found among isolates from specimens of skin and skin structure (pus, wound, or abscess).

Organisms resistant to linezolid via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross resistant to tedizolid (20). However, the presence of the chloramphenicol-florfenicol resistance (*cfr*) gene did not result in resistance to tedizolid in the absence of chromosomal mutations found in some *S. aureus* strains tested (20). Further evaluation is needed to find the molecular mechanism for the differences of susceptibility to linezolid and tedizolid among *S. anginosus* group isolates.

In summary, tedizolid exhibited 2- to 4-fold better *in vitro* activities than linezolid against a variety of Gram-positive cocci associated with ABSSSIs and pneumonia. The decreased activities of tedizolid against isolates of *S. anginosus* and *S. constellatus* in Taiwan need further evaluation.

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